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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/676,340	SUBJECK ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,16-23,33,34 and 46-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,16-23,33,34,46-67 and 69* is/are rejected.

7)☒ Claim(s) *68* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10, 16-23, 33, 34, 46-69 are pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The rejection of claims 1-6, 16, 17, 33, 58, 59, 60 , 61 and 63 under 35 U.S.C. 102(b) as being anticipated by Mizzen et al (WO 98/23735) is maintained for reasons of record.

Claim 1 is drawn to a pharmaceutical vaccine composition comprising an isolated stress protein complex and a physiological acceptable carrier, wherein the stress protein complex comprises an hsp110 polypeptide and an immunogenic polypeptide. Claim 2 embodies the pharmaceutical composition of claim 1 wherein the hsp110 polypeptide is complexed with the immunogenic polypeptide. Claim 3 embodies the pharmaceutical composition of claim 2, wherein the hsp110 polypeptide is complexed with the immunogenic polypeptide by non covalent interaction. Claim 4 embodies the pharmaceutical composition of claim 2, wherein the complex comprises a fusion protein. Claim 5 embodies the pharmaceutical composition of claim 1, wherein the complex is derived from a tumor. Claim 6 embodies the pharmaceutical composition of claim 1, wherein the complex is derived from a cell infected with an infectious agent. Claim 16 embodies the pharmaceutical composition of claim 1, wherein the immunogenic polypeptide comprises a cancer antigen. Claim 17 embodies the pharmaceutical composition of claim 16, wherein the immunogenic polypeptide comprises a her 2/neu peptide.

Claim 33 is drawn to a method for inhibiting tumor growth in a subject comprising administering to said subject an effective amount of the pharmaceutical composition of clam 16 to elicit an anti-tumor immune response in the subject, and thereby inhibiting tumor growth in the subject. Claim 58 embodies the method of claim 33 wherein the hsp110 polypeptide is complexed with the immunogenic polypeptide. Claim 59 embodies the method of claim 33 wherein the hsp110 polypeptide is complexed with the immunogenic polypeptide by non-covalent interaction. Claim 60 embodies the method of claim 33 wherein the complex of the pharmaceutical composition comprises a fusion protein. Claim 61 embodies the method of claim 31 wherein the complex of the pharmaceutical composition is derived from a tumor. Claim 63

embodies the method of claim 33 wherein the immunogenic polypeptide of the pharmaceutical composition comprises a her2/neu peptide.

Mizzen et al disclose a vaccine for inducing cell-mediated immunity comprising one or more stress proteins and one or more antigens (page 10, lines 9-23), wherein the preferred antigens are tumor associated antigens (page 6, lines 12-24) and that useful tumor associated antigens are her2/neu (page 14, lines 16-18) and influenza antigens (page 5, line 5 to page 6, line 8). Mizzen et al contemplates that the vaccines comprise mixtures of antigens and stress protein, conjugates of antigens and stress proteins and fusion proteins comprising antigens and stress proteins (page 12, lines 2-20). Mizzen et al disclose the stress protein of Hsp110 as an example of the stress proteins of the invention (page 23, lines 6-10). Mizzen et al disclose the pharmaceutically acceptable carrier of 2mM sodium phosphate and 150mM NaCl at pH 7 (page 41, lines 4-7). Mizzen et al generally teach that the vaccines comprising stress proteins and an antigen are useful in the treatment of a bacterial pathogen in a mammal (page 12, lines 29-32), thus fulfilling the specific embodiments of claim 6.

4. The rejection of claims 1-8, 16, 17, 33, 58-63 under 35 U.S.C. 103(a) as being unpatentable over Mizzen et al (WO 98/23735) in view of the abstract of Wang et al (FEBS Letters, 1999 February, Vol. 464, pp. 98-102) is maintained for reasons of record. The specific embodiments of claims 1-6, 16, 17, 33, 58, 59, 60 , 61 and 63 are set forth above. Claim 7 embodies the pharmaceutical composition of claim 1, wherein the stress protein complex further comprises a polypeptide selected from the group consisting of hsp70, hsp90, grp78 and grp94. Claim 8 embodies the pharmaceutical composition of claim 1, wherein the stress protein complex comprises hsp110 complexed with hsp70 and hsp25. Claim 62 embodies the method of claim 33 wherein the hsp110 is complexed with hsp70 and hso25.

Mizzen et al teach the specific embodiments of claims 1-6, 16, 17, 33, 58, 59, 60 , 61 and 63 for the reasons set forth in the section above. Mizzen et al generally teach that the vaccines comprising stress proteins and an antigen are useful in the treatment of a bacterial pathogen in a mammal (page 12, lines 29-32) and that the stress proteins of Hsp70 and Hsp20-30 are among the major determinants recognized in the immune response to infection by M. tuberculosis (page

21, lines 18-22). Mizzen et al do not specifically teach a vaccine composition comprising hsp110 complexed to hsp70 and hsp25.

The abstract of Wang et al teach that native Hsp110 forms a complex with Hsp25 and Hsp70 (lines 7-9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use a pharmaceutical composition comprising a complex of hsp110, hsp25 and hsp70 proteins as a vaccine for M tuberculosis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mizzen et al on (a) pharmaceutical compositions comprising heat shock proteins such as Hsp110 for the treatment of a bacterial pathogens and (b) the immunogenicity of the Hsp25 and Hsp70 proteins produced by an M tuberculosis infection, and the teachings of Wang et al on the native interaction of the Hsp110, Hsp25 and Hsp70 proteins. One of skill in the art would recognize that the heat shock proteins of Hsp25 and Hsp70 proteins are antigens produced by the intracellular M tuberculosis pathogen, and would be therefore motivated in using said proteins in a vaccine against tuberculosis.

5. The rejection of claims 1-6, 16, 17, 23, 33, 58, 59, 60 , 61, 63 and 69 under 35 U.S.C. 103(a) as being unpatentable over Mizzen et al (WO 98/23735) in view of Srivastava et al (WO 95/24923) and either of Dong et al (Pharmaceutical Biotechnology, 1995, Vol. 6, pp. 625-643) or Heath, Pharmaceutical Biotechnology, 1995, Vol. 6, pp. 645-658) is maintained for reasons of record. The specific embodiments of claims 1-6, 16, 17, 33, 58, 59, 60, 61 and 63 are set forth above. Claim 23 embodies the pharmaceutical composition of claim 1, further comprising an adjuvant. Claim 69 embodies the method of claim 33 wherein the pharmaceutical composition further comprises an adjuvant. Mizzen et al teach the specific limitations of claims 1-6, 16, 17, 33, 58, 59, 60 , 61 and 63 for the reasons set forth above. Mizzen et al do not teach a pharmaceutical composition comprising hsp110 in combination with an adjuvant.

Srivastava et al teach vaccines comprising stress protein-peptide complexes and cytokines (abstract and page 48, lines 16-21). Either of Dong et al or Heath et al identify cytokines as immunological adjutants.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the vaccine taught by Mizzen et al with a cytokine as an adjuvant.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teaching of either Dong et al or Heath on the efficacy of cytokines as immunological adjutants and the teachings of Srivastava et al on the combination of stress-protein-peptide vaccines with cytokines for the initiation of cytotoxic T-cell response against said peptide.

6. The rejection of claims 1-6, 16-18, 33, 58, 59, 60 , 61, 63 and 64 under 35 U.S.C. 103(a) as being unpatentable over Mizzen et al (WO 98/23735) in view of Cheever et al ((U.S. 5,726,023) is maintained for reasons of record. The specific embodiments of claims 1-6, 16, 17, 33, 58, 59, 60, 61 and 63 are set forth above. Claim 18 embodies the pharmaceutical composition of claim 17, wherein the her 2/neu peptide is derived from the intracellular domain of her 2/neu. Claim 21 embodies the composition of claim 16 wherein the cancer antigen is a colon cancer antigen.. Claim 64 embodies the method of claim 63 wherein the her2/neu peptide is derived form the intracellular domain of her2/neu. Mizzen et al disclose a vaccine for inducing cell-mediated immunity comprising one or more stress proteins and one or more antigens (page 10, lines 9-23), wherein the preferred antigens are tumor associated antigens (page 6, lines 12-24) and that useful tumor associated antigens are her2/neu (page 14, lines 16-18). Mizzen et al do not specifically teach the intracellular domain of said protein.

Cheever et al teach that rats immunized with the intracellular domain (ICD) of Her2 developed higher levels of Neu peptide specific T-cell responses as well as Neu protein specific T-cell responses in contrast to rats immunized with the extracellular domain (ECD) of Her2 (column 30, line 47 to column 32, line 8). Cheever et al teach that the expression of Her-2/neu is associated with colon cancer (claim 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the ICD as the tumor-associated antigen in the vaccine taught by Mizzen et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Cheever et al on the advantages of eliciting an immune response against the ICD of Her2/neu versus the ECD of Her2/neu.

7. The rejection of claims 1-6, 16-18, 20, 21, 33, 58, 59, 60 , 61, 63 and 64 under 35 U.S.C. 103(a) as being unpatentable over Mizzen et al (WO 98/23735) and Cheever et al ((U.S. 5,726,023) as applied to claims 1-6, 16-18, 33, 58, 59, 60 , 61, 63 and 64 above, and further in view of Eberlein et al (U.S. 5,550,214) is maintained for reasons of record.

The specific embodiments of claims 1-6, 16, 17, 33, 58, 59, 60, 61 and 63 and the teachings of Mizzen and Cheever which render these claims obvious is set forth above. Claim 20 embodies the pharmaceutical composition of claim 17 wherein the her-2/neu peptide is derived from the transmembrane region of her-2/neu Cheever et al teaches compositions comprising either the transmembrane domain or the extracellular domain of her-2/nei. Neither Mizzen et al nor Cheever et al teach a composition comprising the transmembrane region of Her-2/neu.

Eberlein et al teach immunogenic peptides derived from Her-2/neu and the presentation of said peptides by HLA-A2 molecules leading to recognition by cytotoxic T-lymphocytes. This invention is based, in part, on our discovery that HER2/neu antigenic peptides described herein, when presented by HLA-A2 molecules, are recognized by cancer-specific cytotoxic T lymphocytes from many different tumors.. Eberlein et al specifically teach that at least one of these peptides derived from a fragment of the HER2/neu oncogene protein involves a point mutation found in the transmembrane portion of the tumor-derived HER2/neu protein and is not expressed in normal tissue (column 6, lines 6-17).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the peptide derived from the transmembrane region of Her-2/neu for the intracellular portion of the Her-2/neu protein. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Eberlein on the immunogenicity of peptides derived from fragments comprising a point mutation consistent with oncogenic transformation. One of skill in the art would be motivated to induce a immune response against said transmembrane fragment in order to target transformed cells.

8. The rejection of claims 1-6, 16, 17, 19, 33, 58, 59, 60 , 61 and 63 under 35 U.S.C. 103(a) as being unpatentable over Mizzen et al (WO 98/23735) in view of Hudziak et al (U.S. 6,015,567) is maintained for reasons of record.

The specific embodiments of claims 1-6, 16, 17, 33, 58, 59, 60 , 61 and 63 are set forth above. Claim 19 embodies the pharmaceutical composition of claim 17, wherein the her 2/neu peptide is derived from the extracellular domain of her 2/neu. Claim 65 embodies the method of claim 33 wherein the her2/neu peptide is derived from the extracellular domain of her2/neu. Mizzen et al disclose a vaccine for inducing cell-mediated immunity comprising one or more stress proteins including hsp110 and one or more antigens (page 10, lines 9-23), wherein the preferred antigens are tumor associated antigens (page 6, lines 12-24) and that useful tumor associated antigens are her2/neu (page 14, lines 16-18). Mizzen et al do not specifically teach the extracellular domain of said protein.

Hudziak et al teach a vaccine comprising the extracellular portion of the HER2 molecule which may be combined with suitable adjuvants (column 2, lines 60-63). Hudziak et al teach that many breast cancer patients exhibit amplification of the her2 gene (column 10, lines 14-16) and said patients would be expected to benefit from active specific immunotherapy by provoking an immune response in a patient with an immunogenic form of the extracellular domain of HER2 (column 10, lines 38-43)

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the extracellular domain of HER2 as the tumor-associated antigen in the vaccine taught by Mizzen et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Hudziak et al on the benefits expected in patients having breast cancer characterized by amplification of Her2, and in addition from the teachings of Mizzen et al on compositions comprising stress proteins and tumor antigens such as Her2.

9. Applicant argues against the disclosure of Mizzen maintaining that it is not enabling. Applicant states that if the disclosure of Mizzen et al is enabling for the combination of Hsp110 and an immunogenic peptide, then it must also be enabling for a composition comprising any of

the 45 species of stress proteins disclosed by Mizzen et al. Applicant then points out that Wang et al (Journal of Immunology, Vol. 165, pp. 490-497) as Exhibit B, and Nair et al (Journal of Immunology, 1999, Vol. 162, pp. 6426-6432) as Exhibit C teach away from using Grp78 and protein disulfide isomerase, respectively in immune compositions. This has been consideed but not found persuasive because the evidence of Exhibits B and C were not available to one of skill in the art at the time of filing. Therefore, upon reading the disclosure of Mizzen et al, one of skill in the art would not have reason to doubt that the other stress proteins disclosed by Mizzen et al beyond the working examples would also function in immune compositions as disclosed by Mizzen et al. Applicant has not provided any reference that would teach away from the inclusion of Hsp 110 in an immune composition.

Applicant argues that Hsp110 and Grp170 have been discovered to be better chaperones than hsp70 by virtue of having the ability to bind much larger peptides than Hsp70. this has been consideed but not found persuasive. Applicant is arguing limitations for Hsp110 and Grp170 that are not claim limitations.

10. The rejection of claims 1-6, 16, 17, 22, 33, 58, 59, 60 , 61, 63 and 68 under 35 U.S.C. 103(a) as being unpatentable over Mizzen et al (WO 98/23735) in view of Wallen et al (6,066,716) is withdrawn in light of applicant arguments regarding Wallen et al.

11. The rejection of claims 1-5, 7-10, 16-23, 34 and 46-57 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for eliciting an anti-tumor immune response against a pre-existing tumor in a subject , does not reasonably provide enablement for a method of prophylactic ally generating an anti-tumor immune response before the tumor occurs is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-5, 7-10 and 16-23 encompass vaccines for inhibiting the growth of a tumor in a subject and for the inhibition of cancer in a subject. when given the broadest reasonable interpretation the inhibition of a tumor in a subject reads on the generation of a prophylactic immune response before the tumor occurs. Claim 34 and dependent claims 46-57 are clearly

drawn to the prevention of cancer. The specification is not enabling for the use of the disclosed compositions in the prevention of cancer. This would require administration of the claimed formulations prior to the development of the cancer. However, there is no guidance in the specification for determining the appropriate time prior to the development of malignancy to begin the therapy or for identifying patients at risk for developing malignancy. The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

12. Applicant argues that the specification if fully enabling for prophylactic immunization before the transplantation of tumors. Applicant has provided post-filing date reference of Manjili et al (Journal of Immunology, 2003, Vol. 171, pp. 4054-4061) as Exhibit A which supports this concept. Applicant's arguments have been considered but not found persuasive. The reference and the evidence provided in the specification is not commensurate in scope with the instant claims which encompass the administration of the vaccine before the tumor occurs naturally in a patients as differentiated from before the tumor occurs as a result of transplantation of tumor cells into an experimental animal. Thus, the claims are not enabled for the prevention of cancer in a patient which is not an experimental animal for the reasons set forth above. Amendment of the claims to delete the word "vaccine" would overcome the above rejection.

13. Claim 68 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. All other rejections and objections as set forth in the prior Office action are withdrawn in light of applicants arguments and amendments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
9/7/2004

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER